

## **TAU OR A BETA IMMUNOTHERAPY IN AD?**

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For more than 30 years, neurobiologists have known that two proteins, A beta and tau, are the main components involved in the progressive destruction of the human brain in Alzheimer disease (AD). The first is located in the so-called amyloid plaques outside dead and dying cells, whereas a hyperphosphorylated form of tau is consistently present among the various proteins which form neurofibrillary tangles (NFT). Whether A beta or tau is at the origin of neuron death in Alzheimer disease is an old and possibly quite academic debate. The tide began to swing in favour of A beta after the description of mutations in the APP, PS1 and PS2 genes, all related to A beta metabolism, in some rare hereditary early-onset AD cases. Indeed, no mutations in tau gene have been described in AD and it is plausible that at least in some cases A beta-linked abnormalities initiate brain loss. However, four arguments point to the key role of tau in the development of clinically overt dementia. First, several clinicopathological correlations showed that NFT numbers in restricted cortical areas but not amyloid load are related to the severity of dementia. Second, mutations in the tau gene cause some cases of frontotemporal dementia in the absence of A beta deposits. Third, studies in mice carrying APP mutations and varying numbers of the mouse tau gene demonstrated that the absence of tau prevents the behavioural deficits without effect on amyloid deposition. Finally, in a mouse model carrying both plaques and NFT produced by genetic engineering, learning and memory problems improve only after reduction of tau (but not A beta). Interestingly, learning interventions and dietary intake of omega-3 fatty acids decrease the activity of enzymes that phosphorylate tau in these mice.

To date, several labs attempt to develop therapeutic strategies to reduce soluble tau forms including immunological approaches, stabilization of microtubules and inhibition of kinases. Moving away the debate of the "primum movens", AD research takes a closer look to tau as the main player of cognitive decline in various forms of dementia.